PB 274 741

PUBLICATION

85

TOXICOLOGY PROGRAM
Technology Branch
Communicable Disease Center
Atlanta 22, Ga.

ISOTOPE-LABELED INSECTICIDES

# Synthesis of Carbon-14–Labeled Aldrin and Dieldrin

ROGER M. McKINNEY and GEORGE W. PEARCE

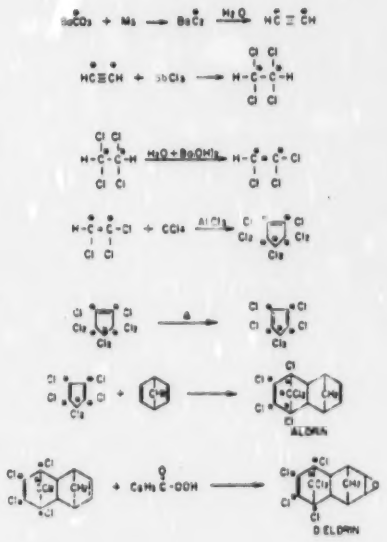
Communicable Disease Center, Public Health Service, U. S. Department of Health, Education, and Welfare, Savannah, Ga.

The insecticides 1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4-*endo*-exo-5,8-dimethanonaphthalene (aldrin) and 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,-8a-octahydro-1,4-*endo*-exo-5,8-dimethanonaphthalene (dieldrin) were prepared labeled with carbon-14. They were synthesized by labeling hexachlorocyclopentadiene and subsequent reaction with 2,5-norbornadiene. Starting with $BaC^{14}O_3$, a 28% yield of aldrin (melting point 102.5° C.) and a 22% yield of dieldrin (melting point 181° C.) were obtained. The specific activities were 3.6 and 3.5 ± 0.1 mc. per gram for aldrin and dieldrin, respectively.

During studies at this laboratory on the fate of aldrin and dieldrin in susceptible and resistant strains of insects and in higher animals it became evident that the chemical methods now available for these compounds are not adequate, especially when an attempt is made to account fully for the dosage applied. It was obvious that $C^{14}$-labeled aldrin and dieldrin would be a great aid in our studies and, accordingly, their synthesis was undertaken. The present paper is a report on this work.

Aldrin is ordinarily prepared by the Diels-Alder reaction of hexachlorocyclopentadiene with 2,5-norbornadiene (bicyclo[2.2.1]hepta - 2,5 - diene), and dieldrin is prepared by the peracid oxidation of aldrin. The problem was to prepare either hexachlorocyclopentadiene or 2,5-norbornadiene with a $C^{14}$ label. Synthesis of $C^{14}$-labeled hexachlorocyclopentadiene appeared to be the most promising approach.

The following six- and seven-step reaction scheme was used in the synthesis of $C^{14}$-labeled aldrin and dieldrin:




Carbon-14 labeled acetylene was prepared by a modification of the method of Cramer and Kistiakowski (*2*). The yields were approximately 70%, as determined by gas volumetric measurements with inactive runs.

The labeled acetylene was converted to tetrachloroethane by treatment with a mixture of antimony pentachloride and trichloride. This reaction as given by Krall (*3*) was found to give very low yields. After the acetylene had been complexed with the antimony pentachloride, it was necessary to decompose the complex by heating for a much longer period of time than that used by Krall to obtain satisfactory yields. With inactive acetylene, 85% yields were consistently obtained in this reaction.

Trichloroethylene was prepared by refluxing the tetrachloroethane with barium hydroxide and steam-distilling the product. Yields of 85 to 90% were obtained with inactive trichloroethylene.

Octachlorocyclopentene was prepared from the trichloroethylene by the method of Prins (*4*). This reaction gave a 70% yield.

The dechlorination of octachlorocyclopentene to hexachlorocyclopentadiene and the subsequent conversion to aldrin and dieldrin were based on

Reprinted from **AGRICULTURAL AND FOOD CHEMISTRY,** Vol. 8, No. 6, Page 456, Nov./Dec. 1960
Copyright 1960 by the American Chemical Society and reprinted by permission of the copyright owner

methods described by Burton, Potter, and Silverman (*1*). The dechlorination was found to be essentially quantitative and the Diels-Alder reaction gave 70 to 75% yields. Oxidation of aldrin to dieldrin gave a 63% yield after two crystallizations.

### Experimental

**Tetrachloroethane, $C^{14}HCl_2C^{14}HCl_2$.** A mixture of 0.59 gram of barium carbonate containing 39 mc. of activity and 19.5 grams of inactive barium carbonate was mixed with 48.6 grams of 70- to 80-mesh magnesium. This was placed in a stainless steel reaction bomb, which later was used as the acetylene generator (*A*, Figure 1). The bomb was sealed with a copper gasket and screw cap fitted with inlet and outlet tubes. The reaction was carried out under a helium atmosphere, the bomb being heated at 725° C. for 15 minutes.

After cooling to room temperature the screw cap of the bomb was replaced by another screw cap with a male 40/50 standard-taper joint and rubber O-ring. This was immediately put into position as the acetylene generator (*A*, Figure 1). The system (Figure 1) was purged with dry nitrogen to remove moisture and oxygen before the liquid nitrogen Dewar flasks were put in place. After the flasks were put in position, the nitrogen flow was reduced to a rate that was just perceptible, as evidenced by the bubbles produced in the oil (*B*, Figure 1) at the end of the train.

A total of 200 ml. of water was very carefully added through the dropping funnel (*C*, Figure 1) over a 2-hour period, followed by the careful addition of 500 ml. of concentrated hydrochloric acid over another 2-hour period. The acetylene generator was kept cold throughout the addition of water and acid with an ice water bath. The contents were finally refluxed for 15 minutes to drive over the last traces of acetylene. The acetylene was condensed in the liquid nitrogen–cooled traps (*D*, *E*, Figure 1), while any moisture not condensed in the water-cooled condenser was retained by the ice water–cooled trap or the silica gel drying tube (Figure 1).

For chlorinating the acetylene, a solution of 12.0 grams of antimony trichloride and 89.7 grams of antimony pentachloride was placed in the reaction flask (*F*, Figure 2). Traps *D* and *E* with the acetylene were attached to the vacuum train as shown in Figure 2. With *D*, *E*, and *F* immersed in liquid nitrogen, the entire system (Figure 2) was evacuated to 30-micron pressure.

The acetylene was then vacuum-transferred to the chlorinating flask, *F*. With stopcocks *A'* and *B'* closed and *C'*, *D'*, and *E'* open, the acetylene–antimony chloride mixture was allowed to warm up to room temperature. The

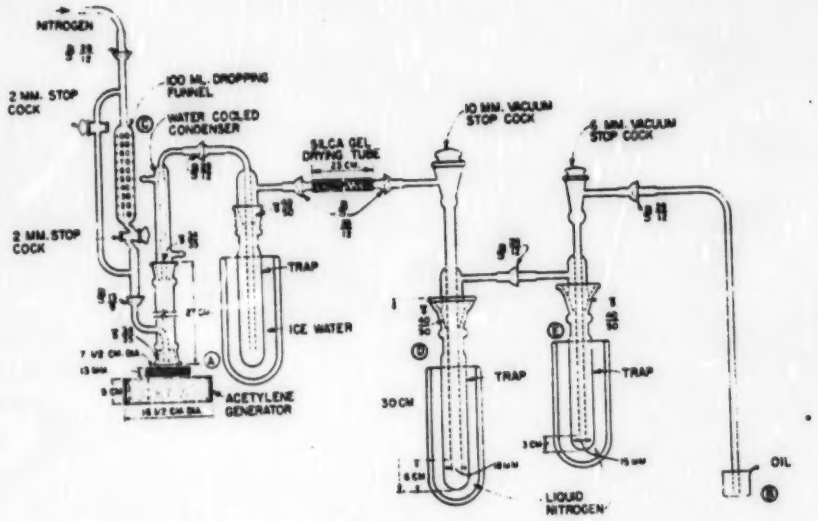



**Figure 1. Acetylene generation apparatus**

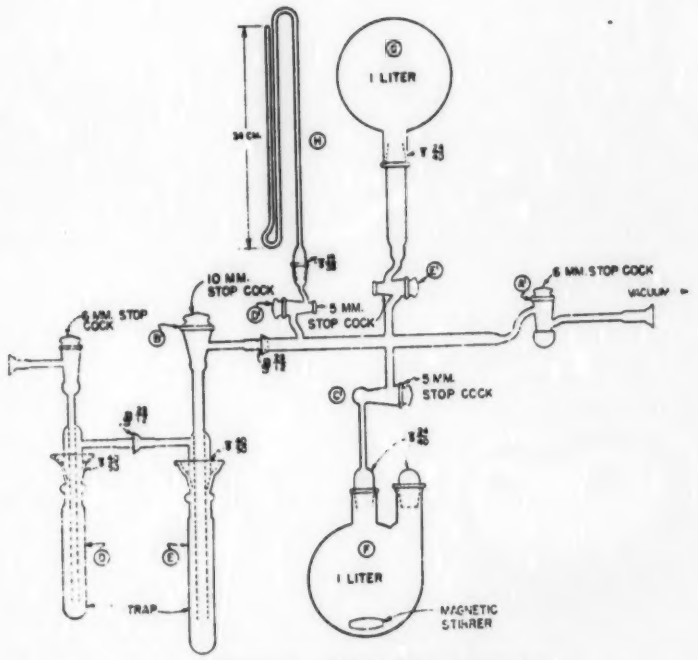



**Figure 2. Chlorination apparatus**

purpose of flask *G* is to add sufficient volume to the system to keep it well below atmospheric pressure. The pressure indicated by manometer *H* at this point was 28 cm., so it was safe to confine the gas in a smaller volume.

The liquid nitrogen bath was replaced on flask *F*, and the acetylene was frozen onto the antimony chloride mixture. With stopcocks *C'* and *D'* open and all other stopcocks closed, the liquid nitrogen bath was removed from flask *F* and replaced by an ice water bath. When the mixture became liquid, it was stirred magnetically and the progress of the absorption of acetylene was followed by the pressure readings. A minimum pressure of 4.4 cm. was reached after 1 hour and the absorption was assumed to be complete.

The liquid nitrogen was again replaced on flask *F* and the remaining gas was frozen. Stopcock *C'* was closed and the reaction mixture was held at 100° C. on a steam bath for 16 hours to bring about complete decomposition of the acetylene–antimony pentachloride complex to produce tetrachloroethane.

The assembly (Figure 2) was modified by removing the 1-liter flask, *G*.

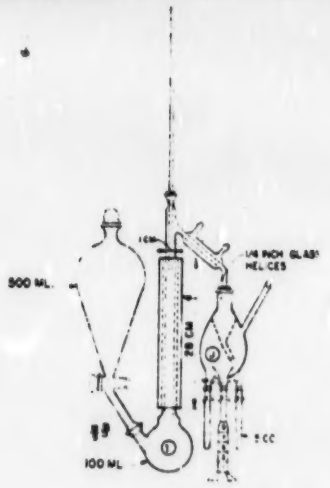



**Figure 3. Distillation apparatus**

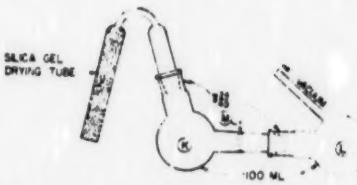



**Figure 4. Recrystallization apparatus**

Traps *D* and *E* were replaced by a ball joint stopper and the stopper in flask *F* was replaced by a 2-necked adaptor with standard-taper joints. A tube containing Ascarite was placed in one neck of the adaptor to serve as a vent, and an Erlenmeyer flask containing 70 grams of calcium hydroxide was attached to the other neck by means of a flexible rubber tube.

An ice bath was placed around flask *F*, and 200 ml. of water were slowly added to the reaction mixture with stirring. This was followed by the careful addition of 70 grams of calcium hydroxide to hydrolyze the antimony chlorides. The tetrachloroethane and some water were then separated from the reaction mixture by direct steam distillation. About 30 ml. of distillate were collected.

**Trichloroethylene.** Tetrachloroethane was dehydrochlorinated by refluxing with water and barium hydroxide. The receiving flask for the steam distillation served as the reaction flask. An additional 40 ml. of water and 10.0 grams of barium hydroxide octahydrate were added to the reaction flask.

The reaction mixture was refluxed for 5 hours and the trichloroethylene and some water were then distilled and collected in a receiver. The yield was 2.5 ml. or 3.7 grams. This is about 56% of the theoretical yield based on barium carbonate.

**Octachlorocyclopentene.** The synthesis of $C^{14}$-labeled trichloroethylene, starting from barium carbonate, was repeated on the same scale and the two batches were combined for a total of 7.4 grams. The trichloroethylene was dried over 6 grams of silica gel and then transferred with the aid of carbon tetrachloride to a 250-ml. dropping funnel. Carbon tetrachloride was added to give a total volume of 170 ml. Two grams of freshly sublimed aluminum chloride and 30 ml. of carbon tetrachloride were placed in a 500-ml., two-necked, round-bottomed flask. The 250-ml. dropping funnel was attached to one neck and a reflux condenser with a drying tube was attached to the other neck.

The reaction mixture was refluxed gently and stirred with a magnetic stirrer throughout the reaction. The trichloroethylene in carbon tetrachloride was added dropwise over a 9-hour period. This was followed by the dropwise addition, over a 2.5-hour period, of 1.74 grams of inactive trichloroethylene in 50 ml. of carbon tetrachloride. The reaction mixture was refluxed for one additional hour and, after cooling, it was filtered with suction through a bed of Celite on a Büchner funnel and received directly in a 500-ml. dropping funnel. The solution was washed three times with 30-ml. portions of water and then mounted in position on the distilling flask, *I*, as shown in Figure 3.

The carbon tetrachloride was removed by flash distillation at atmospheric pressure. When all of the solvent was removed, the fraction cutting adaptor, *J*, was put in position and the product was distilled under reduced pressure. A low-boiling forerun was collected below 75° C. at 0.75-mm. pressure. The fraction distilling above 75° C. at 0.75 mm. was collected as octachlorocyclopentene. A small amount of tarry residue remained in the distilling flask, *I*, at the end of the distillation.

The yield of crude octachlorocyclopentene was 5.4 ml. or 9.89 grams. This was vacuum-transferred to flask *K* of the recrystallizing apparatus shown in Figure 4. Methanol (10 ml.) was added and the product was solidified by cooling in a dry ice–acetone bath and broken up into a fine powder with the use of a glass rod. The methanol was removed while still cold by tilting the apparatus so that the receiver *L* was in an upright position and applying a vacuum. The octachlorocyclopentene was retained on the sintered-glass disk, *M*. The yield of octachlorocyclopentene was 8.68 grams or 72% based on trichloroethylene. This is 44.5% based on barium carbonate.

**Hexachlorocyclopentadiene.** The octachlorocyclopentene was thermally dechlorinated to hexachlorocyclopentadiene by the procedure described by Burton, Potter, and Silverman (*1*). The yield was 6.75 grams. This is 98% based on octachlorocyclopentene and 43.6% based on barium carbonate.

**Aldrin.** Aldrin was prepared by the reaction of hexachlorocyclopentadiene with 2,5-norbornadiene (*1*). The product was distilled at a pressure of 30 microns, giving a yield of 8.48 grams of crude aldrin. The infrared spectrum of this product indicated that it was contaminated with a small amount of isodrin, a geometrical isomer of aldrin. The presence of isodrin was detected by an absorption band at 13.58 microns which is not present in pure aldrin.

To remove the isodrin from the aldrin, the crude product was chromatographed on an alumina column which was 4 cm. in diameter and 115 cm. long. The alumina was Fisher 80- to 200-mesh adsorption grade which was activated by heating at 200° C. *n*-Hexane was used as the eluting solvent. The aldrin was eluted first, 7.3 grams of isodrin-free aldrin being collected. This is 81.0% based on hexachlorocyclopentadiene or 35.3% based on barium carbonate. The succeeding fractions contained a mixture of radioactive isodrin and aldrin. They were combined and reserved for further separation.

The aldrin at this point was almost pure. The infrared spectrum was identical with that of a pure authentic sample and the melting point was 98° C. as compared with 102.5° C. for the authentic sample. A 3.86-gram portion was recrystallized from 11 ml. of isopropyl alcohol with the use of the recrystallizing apparatus shown in Figure 4. Recovery was 3.1 grams of pure radioactive aldrin, melting point 102.5° C. This represents a 65% yield from hexachlorocyclopentadiene and a 28.3% yield from barium carbonate. The specific activity was 3.6 mc. per gram.

**Dieldrin.** Using the method of Burton *et al.* (*1*) as a guide, the following procedure was used to convert aldrin to dieldrin: A 3.96-gram portion of chromatographed, but not recrystallized, radioactive aldrin was placed in a 125-ml. glass-stoppered Erlenmeyer flask. To this were added 70 ml. of 0.5*M* perbenzoic acid in chloroform. The reaction mixture was allowed to stand for 17 hours at 6° C. It was then transferred to a 250-ml. separatory funnel and washed once with 50 ml. of a 10% sodium bisulfite solution, twice with 50 ml. of saturated sodium carbonate solution, and three times with 50 ml. of water. The chloroform solution was transferred to a 300-ml. flask and the solvent was removed with a rotary evaporator. The crude product was vacuum-transferred to the recrystallizing apparatus shown in Figure 4. The transfer was effected by heating the dieldrin to 180° C. at 60-micron pressure.

The product was recrystallized twice from 10 ml. of isopropyl alcohol to give a yield of 2.58 grams of pure dieldrin or 62.6% based on aldrin. The infrared spectrum was identical with that of an authentic sample of pure dieldrin and the melting point, 181° C., was the same as that of the authentic sample. The over-all yield of dieldrin based on barium carbonate was 22%. The specific activity was 1.32 mc. per mmole or 3.5 mc. per gram.

Because 79 mc. of $C^{14}$ in 200 moles of barium carbonate were used, dieldrin with a specific activity of 4.2 mc. per gram would be expected. However, the 19% dilution of radioactive trichloroethylene with inert trichloroethylene in the preparation of octachlorocyclopentene results in a net expected activity of 3.4 mc. per gram. This is in remarkably good agreement with values obtained and indicates that no exchange of $C^{14}$ occurred in any of the reactions involved.


### Acknowledgment

The authors express their appreciation to the Agricultural Research Division, Shell Development Co., Modesto, Calif., and particularly to John C. Potter and William B. Burton of that company for valuable information and suggestions during the course of this work.


### Literature Cited


(1) Burton, W. B., Potter, J. C., Silverman, M., Division of Agricultural and Food Chemistry, 132nd Meeting, ACS, New York, September 1957.
(2) Cramer, R. D., Kistiakowski, G. B., *J. Biol. Chem.* **137**, 549 (1941).
(3) Krall, R. E., Ph.D. thesis, University of Colorado, pp. 132–3, 1956.
(4) Prins, H. J., *Rec. trav. chim.* **69**, 1003–6 (1950).



*Received for review February 26, 1960. Accepted August 1, 1960. Division of Agricultural and Food Chemistry, 136th Meeting, ACS, Atlantic City, N. J., September 1959.*





PRINTED IN U. S. A.